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FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
FETTEROLF, BRANDON J	

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte TAPAS MUKHOPADHYAY, SUNIL CHADA, ABNER MHASHILKAR, and JACK A. ROTH

Appeal 2007-4150
Application 10/043,877
Technology Center 1600

Decided: March 28, 2008

Before TONI R. SCHEINER, DONALD E. ADAMS,
and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 2, 3, 10, 13-19, 21-29, 76, 77, 83-97, and 99-106. We have jurisdiction under 35 U.S.C. § 6(b). We reverse and remand for consideration of the declaration under 37 U.S.C. § 1.131.

STATEMENT OF THE CASE

The claims are directed to methods of treating cancer or causing apoptosis in tumor cells comprising: (1) determining the tumor suppressor status of the cell; and (2) administering a benzimidazole. Expression of the tumor suppressor gene results in inhibition of the cancer when the benzimidazole is administered (*see* claim 100; Spec. 8-9). Benzimidazoles are chemical compounds which are known in the prior art (Spec. 9: 9-11).

Claims 2-8, 10, 11, 13-63, 65-74, 76-160, 163, 166, 168, 171-175 are pending; claims 4-8, 11, 30-63, 65-74, 78-82, 107-160, 163, 166, 168 and 171-175 are withdrawn from consideration; and claims 2, 3, 10, 13-19, 21-29, 76, 77, 83-97 and 99-106 are on appeal (App. Br. 3).

The following rejections are on review:

1) Claims 76, 83-97, and 99-106 under 35 U.S.C. § 103(a) as obvious over Camden '093 (U.S. Pat. No. 6,262,093 B1, Jul. 17, 2001) and Perdomo (*J. Cancer Res. Clin. Oncol.* 124: 10-18, 1998) (Ans. 3);

2) Claim 77 under 35 U.S.C. § 103(a) as obvious over Camden '093, Perdomo, and Delatour (English translation of *Therapie*, 31: 505-515, 1976) (Ans. 5);

3) Claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97, and 100-106 under 35 U.S.C. § 103(a) as obvious over Camden '144 (U.S. Pat. No. 5,880,144, Mar. 9, 1999) and Perdomo, as evidenced by Camden '093 (Ans. 5);

4) Claims 3 and 77 under 35 U.S.C. § 103(a) as obvious over Camden '144, Perdomo, and Delatour or Nasr (*J. Pharmaceutical Sciences*, 74: 831-836, 1985) (Ans. 8); and

5) Claims 13, 14, 86, and 87 under 35 U.S.C. § 103(a) as obvious over Camden '144, Perdomo, and Lucci (*Cancer*, 86: 300-311, 1999) (Ans. 9).

We select claims 22, 100, 77, and 86, which read as follows, as representative.

> 22. A method for inducing apoptosis in a tumor cell expressing a tumor suppressor gene, comprising the steps of:
>
> (1) determining the tumor suppressor gene status of the tumor cell; and
>
> (2) administering an effective amount of a benzimidazole to said tumor cell, wherein expression of the tumor suppressor gene by the tumor cell and benzimidazole results in the apoptosis of the tumor cell.
>
> 100. A method for treating a patient having cancer, wherein cancer cells express a tumor suppressor, comprising the steps of:
>
> (1) determining the tumor suppressor gene status of the cancer cell; and
>
> (2) administering an effective amount of a benzimidazole to said patient, wherein the expression of the tumor suppressor gene by the cancer cell and the administration of the benzimidazole results in the inhibition of said cancer.
>
> 77. The method of claim 100, wherein the benzimidazole derivative is methyl 5-benzoylbenzimidazole-2-carbamate (mebendazole).
>
> 86. The method of claim 100, wherein the cancer cell is a multidrug resistant tumor cell.

OBVIOUSNESS OVER CAMDEN '844

The "[E]xaminer bears the initial burden, on review of the prior art . . , of presenting a prima facie case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). In making an obvious determination, the

Examiner must first identity the scope and content of the prior art and then ascertain the differences between the prior art and the claimed invention. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Thus, we first turn to the prior art. The following numbered findings of fact ("FF") summarize the prior art relied upon by the Examiner in setting forth the basis of the rejection:

Scope and content of the prior art

Camden '144

1. Camden '144 describes a pharmaceutical composition comprising a benzimidazole derivative for treating cancer in humans (Camden '144, at col. 1, ll. 49-57; col. 1, l. 65 to col. 2, l. 64; Ans. 5-6).

2. *In vitro* tests showed benzimidazole derivatives (benomyl, carbendazim, and thiabendazol) were effective in killing tumor cells (Camden '144, at col. 6, l. 38 to col. 7, l. 14; Ans. 5).

3. Camden '144 does not disclose that administration of a benzimidazole derivative causes apoptosis or that its activity is correlated with the status of the tumor suppressor p53 (Ans. 6).

Camden '093

4. Camden '093 describes the same benzimidazole derivatives as in Camden '144.

5. Camden '093 shows that the benzimidazole derivative carbendazim selectively causes apoptosis in tumor cells which express abnormal p53 (Camden '093, at col. 11, l. 65 to col. 13, l. 25; Ans. 6).

Perdomo

6. Perdoma characterizes the relationship between p53 status (a tumor suppressor; Perdomo, at 1, col. 2), radiation, and *in vivo* DNA damage by cisplatin, a DNA cross-linking chemotherapeutic agent (*id.* at 11, col. 1).

7. The "response to cisplatin in vivo of tumors . . . was dependent on p53 status" (*id.* at 17, col. 1, ll. 15-17).

8. Significant regression and apoptosis occurred in treated tumor cells having intact wild-type (normal) p53 ("wt-p53"), but not mutant p53 ("mt-p53) (*id.* at cols. 1-2; Ans. 4). Thus, "[i]ntact p53 was necessary to achieve a favorable response" to cisplatin (*id.* at col. 1 (last sentence)).

9. Perdomo concludes that "analysis of p53 status . . . could make it possible to predict the response to therapy in certain patients" (*id* at 17, col. 1)

Delatour

10. Delatour teaches that the benzimidazole derivative mebendazole ("MBDZ") has antimitotic properties and cancer suppressing activity (antitumor) on Ehrlich's tumor (Delatour, at 11; Ans. 8).

Nasr

11. Nasr describes the *in vivo* anticancer activity of benzimidazole derivatives which are carbonates (Nasr, at 834-35; Ans. 8).

Lucci

12. "Lucci et al. teach multidrug resistance modulators and doxorubicin synergize to elevate ceramide levels and elicit apoptosis in drug-resistant

cancer cells, specifically drug resistant human breast cancer cells lines" (Ans. 9)

Specification

13. According to the Specification:

> It is currently believed that BZs exert their cytotoxic effects by binding to the microtubule system and disrupting its function (Lacey, 1988; Friedman and Platzer, 1980). The suggestion that tubulin is a target for BZs has been supported by the results of drug-binding studies using enriched extracts of helminth and mammalian tubulin (Lacey, 1988). Moreover, competitive drug-binding studies using mammalian tubulin have shown that BZs compete for colchicine binding and inhibit growth of L1210 murine leukemia cells *in vitro* (Friedman and Platzer, 1978; Lacey and Watson, 1989).

(Spec. 10: 1-8.)

Differences between the claimed invention and the prior art

Once the scope and contents of the prior art has been determined, the next step is to identify the differences between the prior art and the claimed invention. *Graham*, 383 U.S. at 17. The following numbered findings of fact are pertinent to this issue:

14. Claim 100 is directed to a method of treating a cancer patient in which the cancer cells express a tumor suppressor.

15. The method has two steps.

16. First, the tumor suppressor gene status of the cancer cell is determined.

17. Second, an effective amount of a benzimidazole is administered to the patient, "wherein the expression of the tumor suppressor gene by the cancer cell and the administration of the benzimidazole results in the inhibition of said cancer."

18. Camden '144 describes treating a cancer patient with a benzimidazole derivative (FF 1-2), as in the second step (FF 17) of claim 100.
19. Camden '144 does not describe determining the tumor suppressor status of the cancer cells (FF 3) as recited in the first step (FF 16) of claim 100.
20. However, Perdomo teaches that "analysis of p53 status [a tumor suppressor] . . . could make it possible to predict the response to therapy in certain patients" (Perdomo, at 17, col. 1; FF 9).
21. Claim 22 is directed to a method of treating apoptosis in a tumor cell expressing a tumor suppressor gene.
22. The method has two steps.
23. First, the tumor suppressor gene status of the tumor cell is determined.
24. Second, an effective amount of a benzimidazole is administered to the cell, "wherein expression of the tumor suppressor gene by the tumor cell and benzimidazole results in the apoptosis of the tumor cell."
25. Method claim 22 covers both *in vitro* and *in vivo* treatment.
26. Camden '144 describes administering a benzimidazole derivative to a tumor cell (FF 2), as in the second step (FF 24) of claim 22.
27. Camden '144 does not describe determining the tumor suppressor status of the tumor cells or that the benzimidazole causes apoptosis (FF 3) as recited in the first and second steps, respectively (FF 23-24), of claim 22.
28. However, Perdomo teaches that "analysis of p53 status . . . could make it possible to predict the response to therapy in certain patients" (Perdomo, at 17, col. 1; FF 9).

Reason to combine the prior art

Once the differences between the prior art and the claimed invention have been ascertained, the next step is to identify motivation or a reason why persons of ordinary skill in the art would have been prompted to combine the prior art to have made the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The following findings are relevant to this determination:

29. The Examiner finds that persons of ordinary skill in the art would have been motivated to have modified Camden '144's method by determining p53 (tumor suppressor) status because

> Camden ['093] teaches the selectivity in killing p53 abnormal cell lines versus cells expressing normal p53 . . . , while Perdomo et al. teaches that the "response to cisplatin in vivo of tumors derived from different NSCLC lines was dependent on p53 status . . . ." Further, one of ordinary skill in the art would have a reasonable expectation of success because Perdomo et al. teaches "analysis of p53 status, by immunohistochemical or other methods such as the polymerase chain reaction (PCR), could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph)."

(Ans. 7.)

Analysis

Camden '144 and Perdomo

Claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97, and 100-106 stand rejected under 35 U.S.C. § 103 as obvious over Camden '144 and Perdomo as evidenced by Camden '093 (Ans. 5; *see* Rejection 3 above).

We will not sustain this rejection. The Examiner finds that Camden '093 provides the motivation to have modified Camden '144 with Perdomo's teachings about p53 status (Ans. 7; FF 29). This is clearly an error since the rejection is based on Camden '144 and Perdomo. Camden

'093 was relied upon for inherency – i.e., that the benzimidazole derivatives described in Camden '144 cause apoptosis (Ans. 5-6; FF 4-5) (as recited in claim 22, but not claim 100).

In addition to this, we do not find that Perdomo provides adequate motivation to have modified Camden '144's disclosure by adding a step of determining p53 status, the difference between the cited prior art and the invention of claims 100 and 22 (FF 14-28, particularly, FF 19, 27). Perdomo teaches that p53 status is relevant to the therapeutic efficacy of cisplatin – a DNA cross-linking agent (FF 6-9, 20, 28). The Specification states that benzimidazole derivatives exert their cytotoxic effect by a different mechanism (Spec. 10: 1-8; FF 13). We agree with Appellants that Perdomo's teaching that the efficacy of a DNA cross-linking agent depends on the cancer cell's p53 status would not have reasonably suggested to persons of ordinary skill in the art that it would also predict the efficacy of a benzimidazole, which appears to exert its therapeutic effect through a different cellular mechanism (App. Br. 20-21).

For the foregoing reasons, we reverse the rejection of claims 2, 10, 15-19, 21-29, 76, 83, 85, 88-97, and 100-106.

Camden '144, Perdomo, and Delatour or Nasr

Claims 3 and 77 stand rejected under 35 U.S.C. § 103 as obvious over Camden '144, Perdomo, and Delatour or Nasr (Ans. 8; *see* Rejection 4 above).

Claim 77 is directed to the method of claim 100, but where the benzimidazole is mebendazole. Claim 3 is the same, but is dependent on

claim 2. The Examiner finds that Delatour teaches that mebendazole has antitumor properties (Delatour, at 11; Ans. 8; FF 10), and thus persons of ordinary skill in the art would have had reason to have used it in Camden '144's method (Ans. 8). Nasr is relied upon for its teaching of the anticancer activity of benzimidazole carbonates (Nasr, at 834-35; Ans. 8; FF 11).

As neither Delatour nor Nasr provide any suggestion to determine the tumor suppressor status of a cancer in combination with administering mebendazole, we conclude there would have been no reason to combine the cited prior to have made the claimed invention. We reverse the rejection of claims 3 and 77.

Camden' 144, Perdoma, and Lucci

Claims 13, 14, 86, and 87 stand rejected under 35 U.S.C. § 103 as obvious over Camden '144, Perdomo, and Lucci (Ans. 9; *see* Rejection 5 above).

Claim 86 (as is claims 13, 14, and 87) is directed to the method of claim 100, but further limited the cancer cell to a multidrug resistant tumor cell. The Examiner finds that Lucci describes treatment of drug resistant cancer cell lines (FF 12).

As Lucci does not provide any suggestion to determine the tumor suppressor status of a cancer in combination with administering a benzimidazole, we conclude there would have been no reason to combine the cited prior to have made the claimed invention. We reverse the rejection of claims 13, 14, 86, and 97.

OBVIOUSNESS OVER CAMDEN '093

Claims 76, 83-97, and 99-106 stand rejected under 35 U.S.C. § 103(a) as obvious over Camden '093 and Perdomo (Ans. 3; *see* Rejection 1 above); and Claim 77 stands rejected under 35 U.S.C. § 103(a) as obvious over Camden '093, Perdomo, and Delatour (Ans. 5; *see* Rejection 2 above).

Appellants contend that the Camden '144 is not available as prior art under 35 U.S.C. § 102(e) as they "have demonstrated conception and reduction to practice prior to the filing date of" Camden '093 (App. Br. 5).

The Examiner contends that the Third Declaration of Tapas Mukhopadhyay, Sunil Chada, Abner Mhashilkar, and Jack A. Roth, provided to antedate Camden '144, is unacceptable because the claims are directed to "the same patentable invention or an obvious variant" as claimed in the patent (Ans. 12). The Examiner does not explain why the pending claims are directed to "the same patentable invention or an obvious variant" as the Camden '144 claims (*id.*). However, the Examiner contends this determination is made by the "one-way" test (*id.*), i.e., where the invention defined in a claim in the application would have been anticipated by, or an obvious variation of, the invention defined in a claim in the patent. The Examiner cites M.P.E.P. 804 in support of this proposition (*id.*).

The Examiner erred in applying the one-way test to determine whether there is interfering subject matter between the instant claims and those of Camden '144.

According to 37 C.F.R. § 1.131(a), "[p]rior invention may not be established under this section if . . . : (1) The rejection is based on a U.S. patent . . . which claims the same patentable invention as defined in

§ 41.203(a) of this title, in which case an applicant may suggest an interference." § 41.203 states that an "interference exists if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party *and vice versa*." (Emphasis added.) In other words, it must be determined: (1) whether the subject matter of the application claim, when treated as prior art, would have anticipated or rendered obvious the patent claim; *and* ["vice-versa"] (2) whether the subject matter of the patent claim, when treated as prior art, would have anticipated or rendered obvious the application claim. *See* M.P.E.P. 2301.03; *Medichem S.A. v. Rolabo S.L.*, 353 F3d 928, 932 (Fed. Cir. 2003); *Eli Lilly & Co. v. Bd. of Regents of the Univ. of Wa.*, 334 F.3d 1264, 1269-70 (Fed. Cir. 2003). Thus, the two-way test is required under 37 C.F.R. § 1.131(a) to determine when a patent can not be antedated by a declaration.

The one-way test referred to M.P.E.P. 804 is appropriate only for double-patenting determinations, involving patents or applications with at least one common inventor or commonly assigned. These facts have not been stated to be the case for the instant application and Camden '093.

Because the Examiner erred by not applying the correct standard for determining whether prior invention could be established under § 1.131, we *remand* the application to the Examiner in order to properly make that determination under the two-way test. Furthermore, the Examiner should articulate on the record the reason for reaching such a determination so that meaningful review may be made on appellate level.

CONCLUSION

In summary, the rejections of claims 2, 3, 10, 13-19, 21-29, 76, 77, 83, 85-97, and 100-106 over Camden '144 in combination with other prior art are reversed (*see* Rejections 3-5 above). The rejections over claims 76, 77, 83-97, and 99-106 over Camden '093 (*see* Rejections 1-2 above) are remanded to the Examiner.

This application, by virtue of its "special" status, requires an immediate action. MPEP § 708.01(D) (8th ed., rev. 3, August 2005). It is important that the Board be informed promptly of any action affecting the appeal in this case.

REVERSED/REMANDED

Ssc:

FULBRIGHT & JAWORSKI, L.L.P.
600 CONGRESS AVENUE
SUITE 2400
AUSTIN, TX 78701